Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Specific Issues in Antiretroviral Therapy for Neonates (Last updated March 1, 2016; last reviewed March 1, 2016)

Existing pharmacokinetic (PK) and safety data are insufficient for the recommendation of a complete antiretroviral therapy (ART) regimen to treat preterm infants and term infants younger than 15 days (until 42 weeks postmenstrual age).

Until recently, neonatal antiretroviral (ARV) regimens were designed for prophylaxis of perinatal HIV transmission and to be as simple as possible for practical use in resource-constrained countries. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV nucleic acid testing (NAT) results meant that neonatal infections were generally not diagnosed in the first weeks of life. However, because HIV NAT test results now often are available within a few days, HIV-infected infants are being diagnosed as early as the first days of life. In addition, the recent case of prolonged remission of HIV infection in an infant from Mississippi has led to discussions about strategies to achieve prolonged virologic suppression of *in utero* HIV infection with early intensive ARV treatment and subsequent treatment interruption.[1,2] This interest must be tempered by:

- Lack of evidence that very early treatment (before age 2 weeks) will produce a prolonged remission or lead to better outcomes in infected infants
- The very limited dosing and safety data for ARV drugs in the newborn period
- The potential for toxicity from ARV agents.

Sufficient data exist to provide dosing recommendations appropriate for the **treatment** of HIV infection in neonates using the following medications:

- From birth in term and preterm infants: zidovudine
- From birth in term neonates: lamivudine, emtricitabine, and stavudine
- From age 2 weeks in term neonates: didanosine, nevirapine, and ritonavir-boosted lopinavir

For all other ARV drugs, PK and safety data are insufficient to allow recommendations for safe doses appropriate for use in HIV infected neonates.

Data are insufficient on which to base a firm recommendation for treatment doses of nevirapine in newborn infants. Nevirapine PK data in neonates come from studies designed to identify doses appropriate for **prophylaxis**, not treatment, of HIV infection. The target plasma trough concentration in nevirapine perinatal prophylaxis studies was 0.1 microgram/mL, which would be inadequate for sustained therapeutic effect in an HIV-infected individual.[3,4] The weight-based nevirapine dosing regimen used in these prophylaxis studies should be used in infants who require nevirapine for prophylaxis against HIV transmission, rather than treatment for established HIV infection (see Recommended Neonatal Dosing table in the Infant Antiretroviral Prophylaxis section of the Perinatal Guidelines). No neonatal PK data exist for regimens designed to achieve the suggested therapeutic plasma target trough concentration of 3.0 microgram/mL.[5] A population analysis of nevirapine PK data collected during the first year of life combining both prevention studies in the first months of life and treatment studies in older infants demonstrated that nevirapine clearance is low immediately after birth and increases dramatically over the first months of life.[6] Simulations derived from this model suggest that 6 mg/kg of nevirapine administered twice daily to full-term infants (>37 weeks' gestation) in the first 4 weeks of life will maintain trough concentrations above 3.0 microgram/mL. This dosing regimen will be studied in the IMPAACT P1115 clinical trial. Studies of nevirapine PK in premature infants are very limited. A recent study of nevirapine trough concentrations in premature infants receiving daily nevirapine for prophylaxis against HIV transmission demonstrates that nevirapine clearance is further decreased in infants born prematurely.[7] Incorporating these data into the simulations suggests that dosing infants born between 34 and 37 weeks' gestation with 4 mg/kg of nevirapine twice daily for the first week, followed by 6 mg/kg twice daily for the next 3 weeks, should maintain trough concentrations above

3.0 micrograms/mL while avoiding excessive plasma concentrations. This dosing regimen for infants born at 34 to 37 weeks gestation will also be evaluated in P1115. Careful clinical assessment of the infant, evaluation of hepatic and renal function, and review of concomitant medications should be performed when using nevirapine in premature infants.

The experience with ritonavir-boosted lopinavir in neonates highlights the risk of using ARV drugs in neonates without neonatal PK and safety data. Life-threatening cardiovascular, renal, and central nervous system (CNS) toxicity have been reported in 10 infants (8 preterm, 2 term) receiving ritonavir-boosted lopinavir oral solution during the first weeks of life. These toxicities included bradycardia, complete atrioventricular block, heart failure, renal failure, respiratory failure, metabolic acidosis, hypotonia, CNS depression, and one infant died of cardiogenic shock.[8] Lopinavir/ritonavir oral solution contains ethanol (42.4% w/v) and propylene glycol (15.3% w/v), and the contributions of lopinavir, ritonavir, ethanol, and propylene glycol exposure to the observed toxicities are not clear. While a small study of trough lopinavir plasma concentrations in premature infants and a larger-population PK study in infants including neonates provide some preliminary PK data, they are insufficient to currently allow a recommendation for safe and effective lopinavir/ritonavir dosing immediately following birth.[9,10] The Food and Drug Administration recommends against the use of lopinavir/ritonavir oral solution in premature infants until 14 days after their due date, or in full-term infants younger than 42 weeks postmenstrual age.[8]

While there is considerable interest in the use of integrase inhibitors in neonates, data are lacking to formulate a safe dosing recommendation in neonates. Neonatal washout elimination of raltegravir that crossed the placenta after maternal administration is highly variable, with a half-life ranging from 9.3 to 184 hours over the first days of life.[11] As raltegravir competes with bilirubin for protein binding and for elimination through glucuronidation, increased plasma raltegravir concentrations may lead to increased plasma concentrations of free unconjugated bilirubin, posing the risk of bilirubin encephalopathy and kernicterus, particularly in preterm infants who have decreased bilirubin elimination, decreased albumin binding capacity and an immature blood-brain barrier.[12] Use of the recently approved oral granule raltegravir formulation in neonates should be avoided until adequate neonatal PK and safety data are available (see Recommended Neonatal Dosing table in the Infant Antiretroviral Prophylaxis section of the Perinatal Guidelines).

Current recommendations for ARV prophylaxis for prevention of perinatal HIV transmission in high-risk infants in the United States (e.g., limited prenatal maternal ART, high maternal viral load) are for use of zidovudine and nevirapine dosed according to the NICHD-HPTN 040 regimen.[13,14] The nevirapine regimen used in NICHD-HPTN 040 was designed to maintain nevirapine concentrations above 0.1 microgram/mL, the drug concentration target used in studies of prevention of HIV transmission, not the 3.0 microgram/mL target used in treatment of HIV-infected individuals.[15] In this study, both two- and three-drug combination regimens were superior to zidovudine prophylaxis alone to prevent intrapartum transmission; however, there was no incremental benefit of the 3-drug regimen (lamivudine and nelfinavir for 2 weeks plus zidovudine for 6 weeks) compared to the 2-drug regimen (3 doses of nevirapine in the first week of life plus 6 weeks of zidovudine) in prevention of perinatal transmission. The three-drug regimen had significantly more hematologic toxicity and the powder nelfinavir formulation is no longer commercially available.

Despite these data, combination treatment of infants at high risk of HIV infection before diagnostic test results indicating infection are available has been increasing. EPPICC has pooled data from 5,285 mother-infant pairs considered at high risk of perinatal transmission (no antepartum maternal treatment or detectable maternal viremia despite treatment) included in 8 European cohorts and evaluated the use of combination prophylaxis. Among the 1,105 infants receiving combination prophylaxis, 13.5% received zidovudine plus lamivudine, 22.7% received zidovudine plus single-dose nevirapine, 55.8% received zidovudine plus single-dose nevirapine plus lamivudine, and 4.4% received a regimen including a protease inhibitor. In these observational cohorts, there was no difference in infant infection rates between one drug and combination prophylactic regimens.[16] As discussed above, the data necessary for safe and appropriate neonatal dosing of all components of a three-drug ARV regimen for treatment of HIV infection are not currently available.

The risks associated with use of a three-drug ART regimen in neonates as well as the potential benefits, including the possibility of prolonged remission in infected neonates, require further study before a general recommendation can be made. The Panel recommends that neonatal care providers who are considering a 3-drug ART regimen in term infants younger than 2 weeks or premature infants contact a pediatric HIV expert for guidance and individual case assessment of the risk/benefit ratio of treatment and for the latest information on neonatal drug doses. Providers can contact a local pediatric HIV expert or the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on perinatal HIV care.

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